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Hemihypertrophy and a Poorly Differentiated Embryonal Rhabdomyosarcoma of the Pelvis

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Background. Asymmetry of the limbs (conventionally known as hemihypertrophy) is one of the overgrowth syndromes occurring sporadically in the general population at a frequency of approximately 1:86,000. Hemihypertrophy is also reported as part of the Beckwith-Wiedemann syndrome which has as its cardinal features omphalocele, macroglossia and gigantism with hypoglycemia, organomegaly, renal anomalies, hemihypertrophy, and embryonal tumors occurring less frequently. Various neoplasms are also associated with isolated hemihypertrophy. Wilms tumor, adrenocortical carcinoma, and hepatoblastoma are the most frequent. Rhabdomyosarcoma, neuroblastoma, phaeochromocytoma, and undifferentiated sarcoma of the lung are encountered only rarely. Loss of heterozygosity (LOH) of chromosome 11p15.5 is strongly associated with childhood embryonal tumors, particularly Wilms tumor, hepatoblastoma, and rhabdomyosarcoma. ***Procedure and Results.*** In this article, we describe an adolescent male with congenital asymmetry of the lower limbs who presented with a large poorly differentiated pelvic sarcoma. Conventional histologic, immunohistochemical, and ultrastructural studies of this tumor were insufficient for accurate subclassification. However, positive staining for MyoD1 (a recently identified embryonically expressed marker of muscle differentiation) and LOH at the tyrosine hydroxylase locus of chromosome 11p15.5 by molecular analysis favored the diagnosis of embryonal rhabdomyosarcoma over an undifferentiated sarcoma. ***Conclusions.*** This case stresses the importance of pursuing clinical findings when they occur in conditions with an increased risk of developing cancer, which in this case was asymmetry of a limb. Also illustrated by this patient is the need for early consideration of molecular diagnostic tests where available, to refine an uncertain pathologic diagnosis that may ultimately have an impact on treatment and prognosis. Med. Pediatr. Oncol. 32:38–43, 1999.

Key words: hemihypertrophy; sarcoma; rhabdomyosarcoma; LOH; 11p15.5; MyoD1

INTRODUCTION

Asymmetry of the human body has been recognized for centuries by ancient Greek and Roman sculptors and by the early Egyptians. The earliest clinical report of asymmetry of the body is that of Wagner in 1839 [1] who described hemihypertrophy of the right chest and right upper extremity, especially the hand and finger. Since then, many cases have been reported in the world literature and have been the subject of reviews by several authors [2–6], most recently by Cohen [7]. Sporadic cases in the normal population are estimated to occur at a frequency of approximately 1:86,000 [5]. The association of hemihypertrophy with neoplasms is well known, the most common being Wilms tumor [8], with adrenocortical carcinoma [9] and hepatoblastoma [10] also being reported. Other tumors have also been noted rarely, namely neuroblastoma [11,12], testicular carcinoma [13], adrenal adenoma [14], phaeochromocytoma [15], rhabdomyosarcoma [16], leiomyosarcoma [17], and undifferentiated sarcoma of the lung [6]. We encountered an adolescent male with asymmetry of the lower limbs who developed a histologically poorly differentiated sarcoma of the pelvis with features of an embryonal rhabdomyosarcoma.

A 15-year-old African American adolescent male with congenital left-sided hemihypertrophy of the leg and foot (Fig. 1) was referred to the pediatric branch of the National Cancer Institute (NCI) with a 3-month history of left leg pain. It was intermittent, localized to the midthigh, and occasionally felt in the knee. One month after the onset of leg pain, the patient developed a lump in his left buttock with progressive weakness in that leg and

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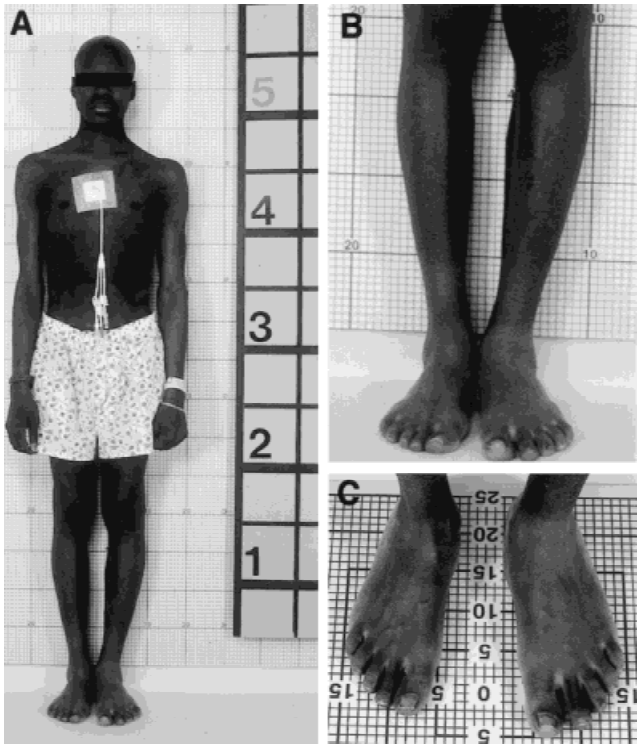

Fig. 1. **A:** The patient with left-sided hemihypertrophy which is most pronounced in the lower limbs (**B**), particularly the feet (**C**).

significant limping. When medical attention was sought, hesitancy of urine along with straining and the passing of small thin stool had developed.

Plain X-ray films of the pelvis revealed a lytic lesion in the left ischium. Magnetic resonance imaging (Fig. 2) showed a pelvic mass of 22 cm in the cephalocaudad dimension, 12 × 12 cm in the anteroposterior and transverse dimensions, respectively, with an isthmus extending through the obturator foramen into the adductors of the left hip. The superior extent of the tumor was to the level of the first sacral vertebra and the inferior extent was to the floor of the pelvis invading the root of the penis. Computed tomography of the chest showed numerous lesions consistent with metastatic pulmonary nodules and a bone scan highlighted a mass arising out of the floor of the pelvis. Bilateral bone marrow aspirates and biopsy revealed no evidence of marrow involvement. Cytogenetic evaluation by G-banding analysis of five analyzable metaphases of the patient showed the 46, XY karyoptype of a normal male.

The patient had been born at full term by spontaneous vaginal delivery with a birth weight of 7 lb 4 oz (50th centile). Apart from noting the left-sided hemihypertrophy, no perinatal problems were reported. An umbilical hernia resolved without intervention. Development was normal, with independent walking at 10 months and speech developing at the expected time. Despite body asymmetry, physical activity was normal.

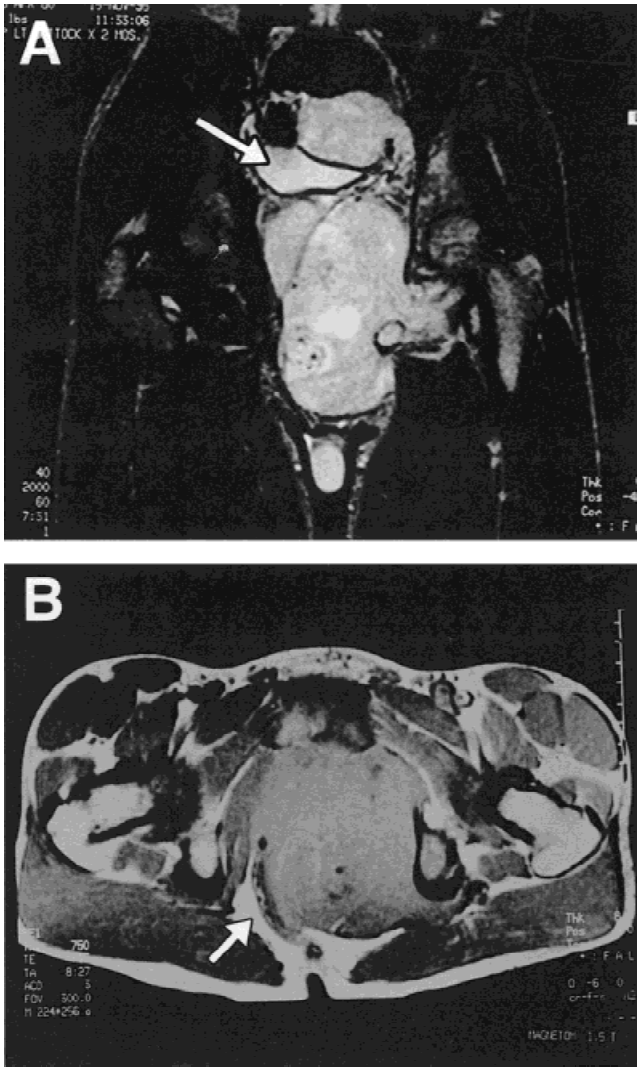

Fig. 2. **A:** Coronal T2 weighted (spin echo TR 2000 and TE 60) image through the femoral heads, showing a large heterogenous pelvic mass extending into the left obturator foramen. The lesion involves the left ischium and displaces the bladder (arrow) superiorly. **B:** Transaxial T1 weighted image (spin echo TR 750 and TE 15) through the level of the obturator foramen showing a pelvic mass extending into the obturator and sciatic foramen. The rectum (arrow) is compressed and displaced to the right.

General examination was significant for icthyosis vulgaris in a slender adolescent of weight 60.7 kg (50th centile), height 172 cm (50th centile), and head circumference 54 cm (25th centile). There were no dysmorphic features. No lymphadenopathy was noted with normal head and neck, cardiovascular, respiratory, and abdominal examination. A left buttock mass measuring 16 × 7.5 cm of firm consistency was noted with gait significant for left leg circumduction but normal power tone and reflexes. Limb measurements revealed differences between the left and right sides. The left leg measured 99 cm and the right 97.5 cm in length. Foot length on the left side 31 cm and on the right 27 cm. Girth of the left foot was

26 cm whereas the right measured 24 cm. The patient was entered on the NCI treatment protocol for high-risk pediatric sarcomas (NCI 86-C-169). Chemotherapy consisted of standard chemotherapeutic agents active against sarcoma, namely, vincristine, etoposide, ifosfamide, doxorubicin, and cyclophosphamide. Radiotherapy to the pelvis (50 Gy) was given between weeks 18 and 24. On completion of chemotherapy and radiotherapy, no evidence of metastases or of pulmonary or pelvic disease was noted. Four months after completing his initial therapy, a pulmonary mass was found. Treatment using a phase one agent (paclitaxel), for a total of three cycles, was given every 3 weeks. This was discontinued because of disease progression. Another phase one agent (9 *cis*-retinoic acid) was commenced, but the disease progressed and he died 24 months from the time of diagnosis.

Family Evaluation

All five half-siblings of the patient were evaluated for body asymmetry and features associated with Beckwith-Wiedemann syndrome. A male half-sibling demonstrated a left ear dimple and pit. A female half-sibling was found to have a generous sized tongue but not macroglossia and a leg length discrepancy of 1 cm. We believe neither of these findings to be strong enough indicators to suggest the diagnosis of Beckwith-Wiedemann syndrome. The remaining members of the family had a normal phenotype.

PATHOLOGY

Needle core biopsy of the buttock mass was performed at the referring institution. The diagnosis of high-grade sarcoma was rendered based on histopathologic evaluation of several pieces of cylindrical segments measuring 0.5 × 0.3 × 0.1 cm. Further diagnostic work-up was not possible due to limited material.

A repeat needle core biopsy was done at the NCI in preference to an open biopsy in view of impending bowel and bladder obstruction. The specimen in aggregate was 0.9 × 0.7 × 0.3 cm. Histologically, very little tumor exhibited hyper- and hypocellular areas, the latter in a myxoid background. The tumor cells were predominantly spindle shaped with scant cytoplasm. Extensive necrosis was present (Fig. 3a). Immunohistochemical staining was negative for keratin, epithelial membrane antigen (EMA), and muscle-specific and smooth muscle actin. Rare cells were positive for desmin and S-100 protein. Neuron-specific enolase was diffusely positive. Further immunohistochemical analysis with an antibody against MyoD1 protein (Novocastra Laboratories Ltd., Newcastle upon Tyne, UK) revealed extensive staining of tumor nuclei (Fig. 3b). Ultrastructurally, the tumor cells were poorly differentiated with variably developed rough endoplasmic reticulum and high nuclear/cytoplasmic ratio. These cells also lacked cytoplasmic filaments and rarely had cytoplasmic glycogen (Fig. 3c,d).

Polymerase chain reaction (PCR)-based studies using polymorphic short tandem repeats at the tyrosine hydroxylase (TH) locus have been used to detect loss of heterozygosity (LOH) at the chromosome 11p15.5 region in human embryonal rhabdomyosarcoma [18]. When analyzed using this technique, tumor material from this patient demonstrated LOH at the TH locus when compared to his normal tissue. Based on the histology of the tumor, ultrastructural findings, and desmin positivity, a rhabdomyosarcoma can only be inferred. However, together with the expression of MyoD1 and the detection of LOH at the TH locus of the 11p15.5 region, a diagnosis of embryonal rhabdomyosarcoma was favored.

DISCUSSION

The present case represents a rare association of sporadic hemihypertrophy and embryonal rhabdomyosarcoma. In a series of 151 patients [17], other embryonal tumors such as Wilms tumor, hepatoblastoma, and neuroblastoma occurred with isolated hemihypertrophy at a frequency of approximately 6%. However, the Intergroup Rhabdomyosarcoma Study Committee reported only one case of hemihypertrophy in a series of 115 patients with rhabdomyosarcoma who were autopsied [16] and no other individual cases have been reported. The classification of hemihypertrophy remains controversial without an internationally accepted definition. Several authors [3,19–22] discuss the need to distinguish true from ‘‘pseudo’’ hemihypertrophy and highlight the association of hemihypertrophy with other conditions. The most notable among them are are Beckwith-Wiedemann syndrome, Klippell-Trenaunay-Weber syndrome, neurofibromatosis, and Proteus syndrome [7]. Asymmetry of the body is regarded by some as a distinct entity, defined as unilateral overgrowth of the body including structures of the head for which no cause can be found, thus excluding disorders of vascular origin and neurofibromatosis [23,24]. An attempt at the subclassification of hemihypertrophy is offered by Rowe [25], whereby complex hemihypertrophy involves an entire half of the body or at least an arm and a leg. When the enlarged parts are on the same side, it is classified as complex ipsilateral; when they are crossed, it is referred to as complex contralateral hemihypertrophy. Also in this classification, simple hemihypertrophy involves a single limb and hemifacial hypertrophy involves one side of the face. The working definition of hemihypertrophy in the NCI Beckwith-Wiedemann Registry is a discrepancy of at least 10% in limb length or girth measurement, which has been used in this case report, although by convention a 10% difference in girth alone is sufficient.

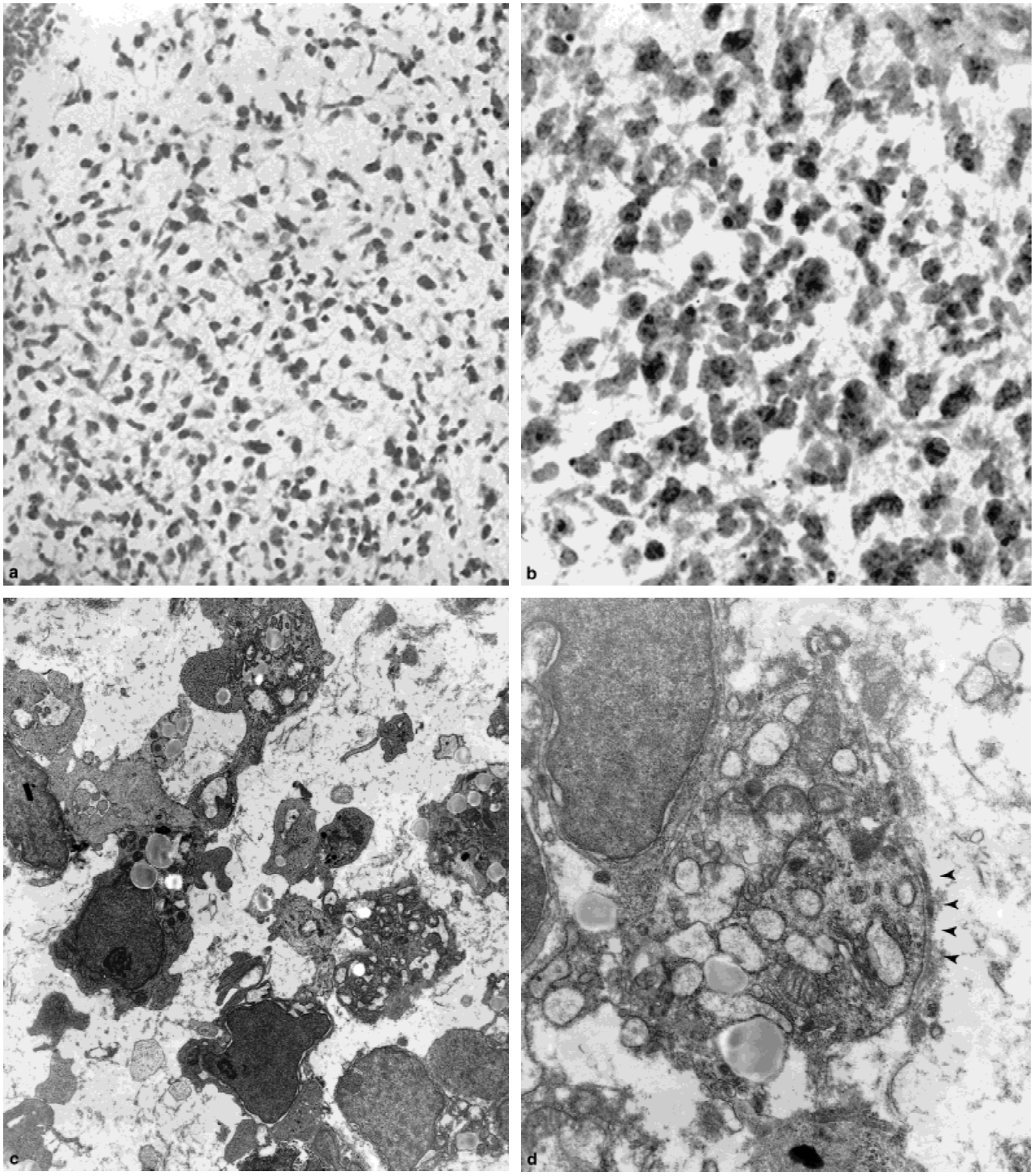

Fig. 3. **a:** The tumor is histologically characterized by spindle-shaped cells with scant cytoplasm in a loose myxoid stroma. Hematoxylin/eosin. ×300. **b:** Discrete nuclear staining for MyoD1 protein is present in almost all tumor cells. Avidin/biotin. ×660. **c:** The tumor cells are poorly differentiated ultrastructurally. ×4,500. **d:** The cytoplasm is scant and contains a few organelles and lipid droplets, but no filaments or Z-bands. There is a focal basal lamina (arrowheads). The latter, though not diagnostic, may be present in primitive myoblasts. ×12,700.

It has also been suggested that hemihypertrophy is an underappreciated diagnostic feature of the overgrowth syndrome of Beckwith-Wiedemann [26]. When probands with Beckwith-Wiedemann syndrome were followed prospectively for risk of malignancy, hemihypertrophy was associated with the greatest relative risk of 4.6 (range 1.5–14.2, confidence interval 95%) [27]. In spite of a left ear crease and pit in a male half-sibling, which

may be observed in patients with Beckwith-Wiedemann syndrome [28], as well as a leg length discrepancy of 1 cm and a generous sized tongue (but not macroglossia) in a female half-sibling, these findings are insufficient to make a diagnosis of Beckwith-Wiedemann syndrome.

The tumor in our patient was not easily classifiable and the traditional histologic and ultrastructural features supported a poorly differentiated sarcoma. The initial differential diagnosis, in addition to an embryonal rhabdomyosarcoma, included other spindle cell sarcomas of the soft tissue as well as an extrarenal Wilms tumor which may present as a monophasic poorly differentiated variant. Limited tumor tissue availability by needle core biopsy was an additional limiting factor for the correct diagnosis. However, the technique of needle core biopsy has been prospectively studied by Barth et al. [29] for its diagnostic utility in soft tissue masses and was expected to yield a definitive diagnosis with the least amount of morbidity. In our patient, the risk of further morbidity from impending bowel and bladder obstruction following laparotomy precluded an open biopsy.

Molecular diagnostic testing on the patient's paraffin-embedded tumor tissue revealed LOH at the 11p15.5 region, as has been reported for Wilms tumor, rhabdomyosarcoma, and hepatoblastoma [30,31]. The same chromosomal region has also been implicated in Beckwith-Wiedemann syndrome with two kindreds showing linkage of the syndrome with the insulin gene located at 11p15.5 [32,33]. Further pedigree analysis of Beckwith-Wiedemann families suggested a pattern of autosomal dominant inheritance with greater penetrance in female offspring, which implies genomic imprinting [34,35]. None of our patient's family members had the constellation of features that is sufficient for the diagnosis of Beckwith-Wiedemann syndrome.

Immunohistochemical studies of the paraffin-embedded tumor tissue revealed positivity for MyoD1 protein. Nuclear staining of MyoD1 is a specific marker for rhabdomyosarcoma [36,37]. Studies by Scrabble et al. [38] on primary tumor and nude mouse xenograft tumor tissue using both the LOH of chromosome 11p15.5 as a molecular marker and MyoD1 positivity showed strong correlation with the diagnosis of embryonal rhabdomyosarcoma. In recent studies, LOH of chromosome 11p15.5 has been observed in a small percent of alveolar rhabdomyosarcomas [39]. However, the combined consideration of histology, MyoD1 staining, and LOH at the 11p15.5 region in this patient's poorly differentiated sarcoma almost undoubtedly supports the diagnosis of embryonal rhabdomyosarcoma.

Hemihypertrophy is a clinical finding associated with cancer predisposition. When present in a child with a mass, it should raise the possibility of an embryonal tumor. LOH at the 11p15.5 region in our patient's tumor together with the positive staining for the early myogenous marker MyoD1 enabled a definitive diagnosis, highlighting the value of considering a patient's phenotype and tumor genotype for an accurate pathologic diagnosis.

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